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CLAIMS

1. A method for the production of an anti-human antigen receptor that is low or not immunogenic in humans comprising the steps of selecting a combination of functionally rearranged VH and VL immunoglobulin chains wherein at least said VH chain is derived from essentially unprimed mature human B-lymphocytes ~~or from essentially anergic human B cells~~ and said VL chain is derived from a naturally occurring human B cell repertoire, said chains being expressed from a recombinant vector and using an in vitro display system for binding to a human antigen.

2. The method according to claim 1 wherein said receptor is an immunoglobulin or a fragment ~~thereof~~.

3. The method according to claim 2 wherein said immunoglobulin fragment is a Fv-fragment.

4. The method according to any one of claims 1 to 3 wherein at least said VH and optionally said VL immunoglobulin chains are derived from a human IgD repertoire.

5. The method according to ~~any one of claims 1 to 4~~ claim 4 wherein said in vitro display system is a phage display system.

6. The method according to ~~any one of claims 1 to 5~~ claim 5 wherein said combination of rearranged chains is expressed from one or more different libraries.

7. The method according to ~~any one of claims 1 to 6~~ claim 6 wherein said human antigen is a tumor antigen.

8. The method according to claim 7 wherein said tumor antigen is the human 17-1A antigen.

9. The method according to claim 8 wherein said VH-chain comprises one of the two sequences shown in Fig. 7 (nucleotides 1 to 381) and Fig. 8 (nucleotides 1 to 339) and/or said VL chain comprises one of the two sequences shown in Fig. 6 (nucleotides 1 to 321) and Fig. 9 (nucleotides 1 to 321).

10. The method according to ~~any one of claims 1 to 9~~ claim 9 wherein said selection step involves

(i) binding of the display vehicle expressing an antigen receptor

(a) on immobilized target antigen or fragments thereof;

(b) on optionally labeled cells expressing the target antigen or fragments thereof;

(c) or to soluble, preferably labeled target antigen or fragments thereof;

(ii) washing off non-specifically binding display vehicle (a and b) and subsequent elution of specifically binding display vehicle

or

(iii) positive enrichment of target antigen bound display vehicle (b and c) from target antigen solution or from suspensions of cells expressing the target antigen;

thus isolated display vehicles including their antigen receptors optionally being multiplied by replication and subjected to further rounds of in vitro selection as described in (i) to (iii).

11. The method according to ~~any one of claims 1 to 10~~ claim 10 wherein prior to said selection step either said VH or said VL chain is selected for binding to said antigen together with a surrogate V chain.

12. The method according to claim 11 wherein said surrogate chain is a mouse VH or VL chain.

13. The method according to ~~any one of claims 1 to 12~~ claim 12 wherein said selection of a suitable combination involves

(a) testing one and the same VH chain in combination with a variety of different VL chains for binding to said human antigen; or

(b) testing one and the same VL chain in combination with a variety of different VH chains for binding to said human antigen.

14. The method according to ~~any one of claims 1 to 13~~ Claim 13 further comprising the steps of obtaining, after selection, the human VH and VL chains or the corresponding nucleic acids and fusing said chains to the same or other VH or VL chains, to immunoglobulin constant regions of heavy (CH) or light chains (CL) or parts thereof or to non-immunoglobulin chains and the corresponding nucleic acids, respectively.

15. The method according to claim 14 wherein said constant region chains are derived from human IgG1 or IgG3.

16. The method according to ~~any one of claims 1 to 13~~ Claim 15 further comprising the steps of obtaining, after selection, the human VH and VL chains and physically linking said chains to non-proteinous pharmaceuticals and/or other biologically active molecules.

17. The method according to ~~any one of claims 1 to 16~~ Claim 16 wherein said VH or VL chains are expressed from nucleic acid sequences that are the result of the RT-PCR amplification of mRNA derived from essentially unprimed mature human B-lymphocytes or from essentially anergic human B-cells.

18. An anti-human antigen receptor that is low or not immunogenic in humans, comprising a combination of functionally rearranged VH and VL chains ~~[preferably]~~ from essentially unprimed mature human B-lymphocytes ~~[or from essentially anergic human B-cells]~~ and said VL chain obtainable by the method according to any one of claims 1 to 17.

19. The receptor according to claims 18 which is an antibody or a fragment thereof.

AMENDED SHEET

wherein at least said VH chain is derived

is derived from a naturally occurring human B cell repertoire, said anti-human antigen receptor being

20. The receptor according to claim 18 or 19 which is specific for a human tumor antigen.

21. The receptor according to claim 20 which is specific for the native human 17-1A antigen.

22. The receptor according to claim 21 wherein said VH chain comprises one of the following two sequences shown in Fig. 7 (nucleotides 1 to 381) and Fig. 8 (nucleotides 1 to 339) and/or said VL chain comprises one of the two following sequences shown in Fig. 6 (nucleotides 1 to 321) and Fig. 9 (nucleotides 1 to 321).

23. A VH chain or ~~a part thereof~~ at least one CDR comprised in the receptor of any one of claims 18 to 22.

24. A VL chain or ~~a part thereof~~ at least one CDR comprised in the receptor of any one of claims 18 to 22.

25. The chain of claim 23 or 24 wherein said ~~part~~ CDR is ~~the~~ CDR3 ~~domain~~.

26. A kit comprising a combination of functionally rearranged VH and VL immunoglobulin chains wherein at least one of the VH and VL chains are derived from essentially unprimed mature human B-lymphocytes, ~~or from essentially anergic human B-cells,~~ said chains being expressible from recombinant vectors of an in vitro display system.

27. The kit according to claim 26 wherein said in vitro display system is a phage display system.

28. An antibody characterized in that it is derived from human sequences, is specific for the native human 17-1A antigen.

29. The antibody of claim 28 which is low or non-immunogenic in humans.

30. The antibody of claim 28 or 29 which is obtainable according to a method of any one of claims 1 to 17.

31. The antibody of any one of claims 28 to 30 recognizing an epitope of the extracellulary domain of the 17-1A antigen preferably comprising at least one amino acid sequence of peptide Nos. 8, 11, 13, 14, 59, 60, 77 and 79.

32. The antibody of any one of claims 28 to 31, wherein the VH chain comprises at least one CDR of one of the following two sequences shown in Fig. 7 (nucleotides 1 to 381) and Fig. 8 (nucleotides 1 to 339) and/or the VL chain comprises at least one CDR of the following two sequences shown in Fig. 6 (nucleotides 1 to 321) and Fig. 9 (nucleotides 1 to 321).

33. A pharmaceutical composition comprising a receptor of any one of claims 18 to 22, a VH chain of claim 23 or 25, a VL chain of claim 24 or 25 and/or antibody of any one of claims 28 to 32, and optionally a pharmaceutically acceptable carrier.